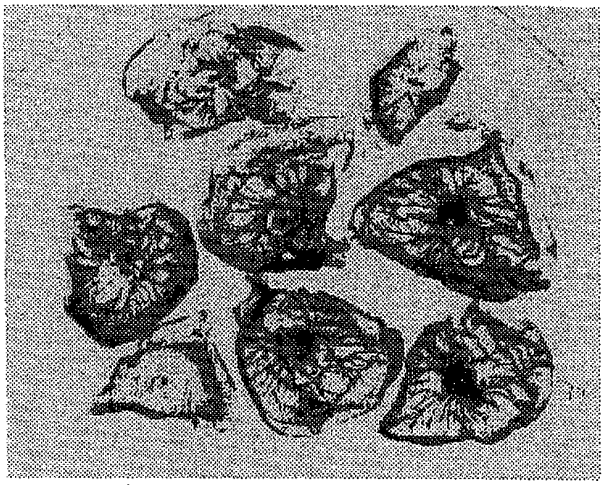
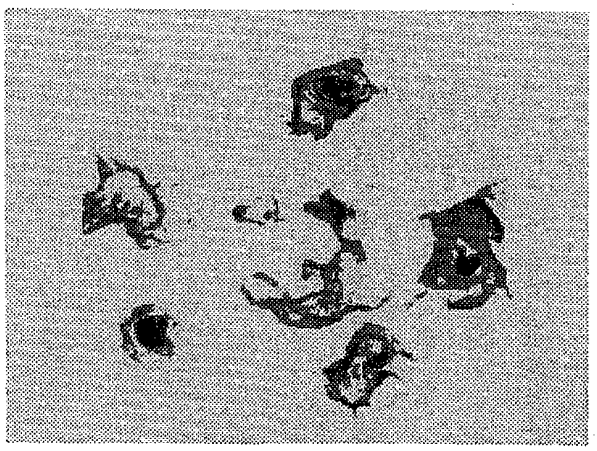
Fig.1A.



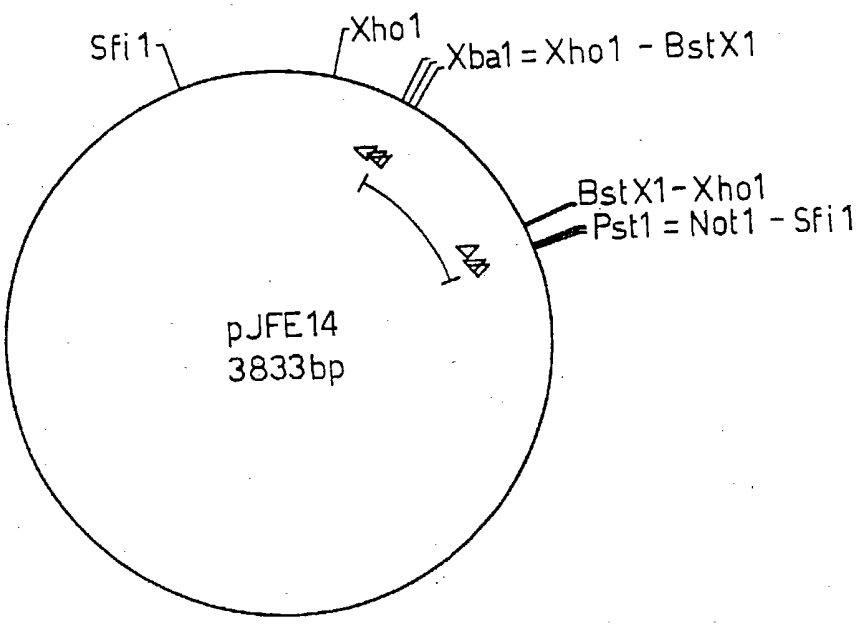
r EHK-1 ecto/h IgG1 Fc
Gelfoam (6ug)

Fig.1B.



r TIE-2 ecto/h IgG1 Fc
Gelfoam (6ug)

Fig.2


Sfi 1
Xho1
Xba1 = Xho1 - BstX1
BstX1 - Xho1
Pst1 = Not1 - Sfi 1
pJFE14
3833bp

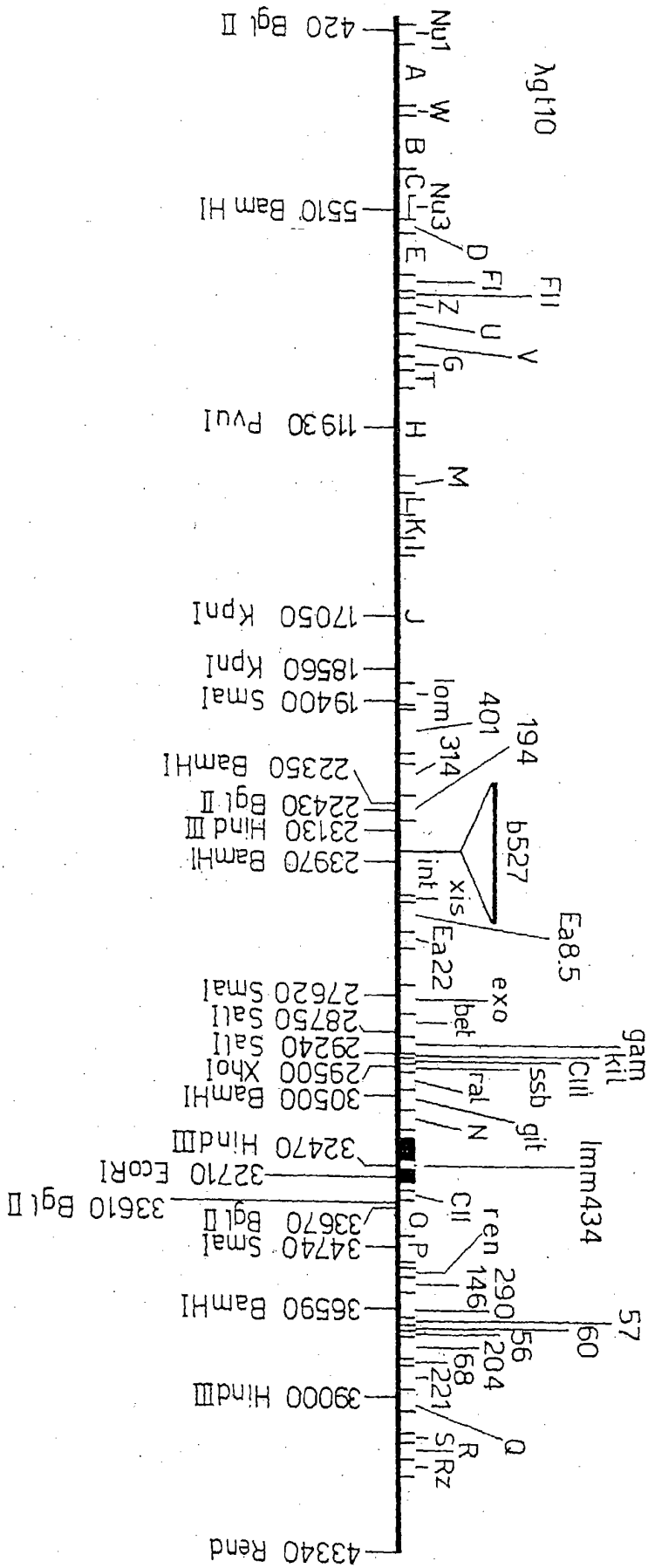

λgt10
420 Bgl II
5510 Bam HI
11930 PvuI
17050 KpnI
18560 KpnI
19400 SmaI
22350 BamHI
22430 Bgl II
23130 Hind III
23970 BamHI
27620 SmaI
28750 SalI
29240 SalI
29500 XhoI
30500 BamHI
32470 HindIII
32710 EcoRI
33610 Bgl II
33670 Bgl II
34740 SmaI
36590 BamHI
39000 HindIII
43340 Rend
Nu1
A
W
B
C
Nu3
D
E
FI
FII
Z
U
V
G
T
H
M
LKI
J
lom
401
314
194
b527
xis
int
Ea8.5
Ea22
exo
bet
gam
kil
CIII
ssb
ral
N
git
Imm434
CII
O
P
ren
290
146
57
60
56
204
68
221
S
R
Q
Rz

Fig.3.

Fig. 4A

```
          10         20         30         40         50         60         70         80
           *          *          *          *          *          *          *          *
CAGCTGACTCAGGCAGGCTCCATGCTGAACGGTCACACAGAGAGGAAACAATAAATCTCAGCTACTATGCAATAAATATC

          90        100        110        120        130        140        150        160
           *          *          *          *          *          *          *          *
TCAAGTTTTAACGAAGAAAAACATCATTGCAGTGAAATAAAAAATTTTAAAATTTTAGAACAAAGCTAACAAATGGCTAG

         170        180        190        200        210        220        230        240
           *          *          *          *          *          *          *          *
TTTTCTATGATTCTTCTTCAAACGCTTTCTTTGAGGGGGAAAGAGTCAAACAAACAAGCAGTTTTACCTGAAATAAAGAA

         250        260        270        280        290        300        310
           *          *          *          *          *          *          *
CTAGTTTTAGAGGTCAGAAGAAAGGAGCAAGTTTTGCGAGAGGCACGGAAGGAGTGTGCTGGCAGTACA ATG ACA GTT
                                                                        M   T   V>

320        330        340        350        360        370
 *          *          *          *          *          *
TTC CTT TCC TTT GCT TTC CTC GCT GCC ATT CTG ACT CAC ATA GGG TGC AGC AAT CAG CGC
 F   L   S   F   A   F   L   A   A   I   L   T   H   I   G   C   S   N   Q   R>

380        390        400        410        420        430
 *          *          *          *          *          *
CGA AGT CCA GAA AAC AGT GGG AGA AGA TAT AAC CGG ATT CAA CAT GGG CAA TGT GCC TAC
 R   S   P   E   N   S   G   R   R   Y   N   R   I   Q   H   G   Q   C   A   Y>
```

Fig. 4B

```
440                 450                 460                 470                 480                 490
*                   *                   *                   *                   *                   *
ACT TTC ATT CTT CCA GAA CAC GAT GGC AAC TGT CGT GAG AGT ACG ACA GAC CAG TAC AAC
 T   F   I   L   P   E   H   D   G   N   C   R   E   S   T   T   D   Q   Y   N>

500                 510                 520                 530                 540                 550
*                   *                   *                   *                   *                   *
ACA AAC GCT CTG CAG AGA GAT GCT CCA CAC GTG GAA CCG GAT TTC TCT TCC CAG AAA CTT
 T   N   A   L   Q   R   D   A   P   H   V   E   P   D   F   S   S   Q   K   L>

560                 570                 580                 590                 600                 610
*                   *                   *                   *                   *                   *
CAA CAT CTG GAA CAT GTG ATG GAA AAT TAT ACT CAG TGG CTG CAA AAA CTT GAG AAT TAC
 Q   H   L   E   H   V   M   E   N   Y   T   Q   W   L   Q   K   L   E   N   Y>

620                 630                 640                 650                 660                 670
*                   *                   *                   *                   *                   *
ATT GTG GAA AAC ATG AAG TCG GAG ATG GCC CAG ATA CAG CAG AAT GCA GTT CAG AAC CAC
 I   V   E   N   M   K   S   E   M   A   Q   I   Q   Q   N   A   V   Q   N   H>

680                 690                 700                 710                 720                 730
*                   *                   *                   *                   *                   *
ACG GCT ACC ATG CTG GAG ATA GGA ACC AGC CTC CTC TCT CAG ACT GCA GAG CAG ACC AGA
 T   A   T   M   L   E   I   G   T   S   L   L   S   Q   T   A   E   Q   T   R>
```

Fig. 4C

```
740             750             760             770             780             790
*               *               *               *               *               *
AAG CTG ACA GAT GTT GAG ACC CAG GTA CTA AAT CAA ACT TCT CGA CTT GAG ATA CAG CTG
 K   L   T   D   V   E   T   Q   V   L   N   Q   T   S   R   L   E   I   Q   L>

800             810             820             830             840             850
*               *               *               *               *               *
CTG GAG AAT TCA TTA TCC ACC TAC AAG CTA GAG AAG CAA CTT CTT CAA CAG ACA AAT GAA
 L   E   N   S   L   S   T   Y   K   L   E   K   Q   L   L   Q   Q   T   N   E>

860             870             880             890             900             910
*               *               *               *               *               *
ATC TTG AAG ATC CAT GAA AAA AAC AGT TTA TTA GAA CAT AAA ATC TTA GAA ATG GAA GGA
 I   L   K   I   H   E   K   N   S   L   L   E   H   K   I   L   E   M   E   G>

920             930             940             950             960             970
*               *               *               *               *               *
AAA CAC AAG GAA GAG TTG GAC ACC TTA AAG GAA GAG AAA GAG AAC CTT CAA GGC TTG GTT
 K   H   K   E   E   L   D   T   L   K   E   E   K   E   N   L   Q   G   L   V>

980             990            1000            1010            1020            1030
*               *               *               *               *               *
ACT CGT CAA ACA TAT ATA ATC CAG GAG CTG GAA AAG CAA TTA AAC AGA GCT ACC ACC AAC
 T   R   Q   T   Y   I   I   Q   E   L   E   K   Q   L   N   R   A   T   T   N>
```

Fig. 4D

```
1040        1050        1060        1070        1080        1090
*           *           *           *           *           *
AAC AGT GTC CTT CAG AAG CAG CAA CTG GAG CTG ATG GAC ACA GTC CAC AAC CTT GTC AAT
 N   S   V   L   Q   K   Q   Q   L   E   L   M   D   T   V   H   N   L   V   N>

1100        1110        1120        1130        1140        1150
*           *           *           *           *           *
CTT TGC ACT AAA GAA GGT GTT TTA CTA AAG GGA GGA AAA AGA GAG GAA GAG AAA CCA TTT
 L   C   T   K   E   G   V   L   L   K   G   G   K   R   E   E   E   K   P   F>

1160        1170        1180        1190        1200        1210
*           *           *           *           *           *
AGA GAC TGT GCA GAT GTA TAT CAA GCT GGT TTT AAT AAA AGT GGA ATC TAC ACT ATT TAT
 R   D   C   A   D   V   Y   Q   A   G   F   N   K   S   G   I   Y   T   I   Y>

1220        1230        1240        1250        1260        1270
*           *           *           *           *           *
ATT AAT AAT ATG CCA GAA CCC AAA AAG GTG TTT TGC AAT ATG GAT GTC AAT GGG GGA GGT
 I   N   N   M   P   E   P   K   K   V   F   C   N   M   D   V   N   G   G   G>

1280        1290        1300        1310        1320        1330
*           *           *           *           *           *
TGG ACT GTA ATA CAA CAT CGT GAA GAT GGA AGT CTA GAT TTC CAA AGA GGC TGG AAG GAA
 W   T   V   I   Q   H   R   E   D   G   S   L   D   F   Q   R   G   W   K   E>

1340        1350        1360        1370        1380        1390
*           *           *           *           *           *
TAT AAA ATG GGT TTT GGA AAT CCC TCC GGT GAA TAT TGG CTG GGG AAT GAG TTT ATT TTT
 Y   K   M   G   F   G   N   P   S   G   E   Y   W   L   G   N   E   F   I   F>
```

Fig. 4E

```
1400          1410          1420          1430          1440          1450
 *             *             *             *             *             *
GCC ATT ACC AGT CAG AGG CAG TAC ATG CTA AGA ATT GAG TTA ATG GAC TGG GAA GGG AAC
 A   I   T   S   Q   R   Q   Y   M   L   R   I   E   L   M   D   W   E   G   N>

1460          1470          1480          1490          1500          1510
 *             *             *             *             *             *
CGA GCC TAT TCA CAG TAT GAC AGA TTC CAC ATA GGA AAT GAA AAG CAA AAC TAT AGG TTG
 R   A   Y   S   Q   Y   D   R   F   H   I   G   N   E   K   Q   N   Y   R   L>

1520          1530          1540          1550          1560          1570
 *             *             *             *             *             *
TAT TTA AAA GGT CAC ACT GGG ACA GCA GGA AAA CAG AGC AGC CTG ATC TTA CAC GGT GCT
 Y   L   K   G   H   T   G   T   A   G   K   Q   S   S   L   I   L   H   G   A>

1580          1590          1600          1610          1620          1630
 *             *             *             *             *             *
GAT TTC AGC ACT AAA GAT GCT GAT AAT GAC AAC TGT ATG TGC AAA TGT GCC CTC ATG TTA
 D   F   S   T   K   D   A   D   N   D   N   C   M   C   K   C   A   L   M   L>

1640          1650          1660          1670          1680          1690
 *             *             *             *             *             *
ACA GGA GGA TGG TGG TTT GAT GCT TGT GGC CCC TCC AAT CTA AAT GGA ATG TTC TAT ACT
 T   G   G   W   W   F   D   A   C   G   P   S   N   L   N   G   M   F   Y   T>
```

Att. Docket No. REG 330G1Z
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Applicant:Davis, et al.
Title: TIE-2 Ligands, Methods of Making and Uses Thereof

Fig. 4F

```
1700          1710          1720          1730          1740          1750
 *             *             *             *             *             *
GCG GGA CAA AAC CAT GGA AAA CTG AAT GGG ATA AAG TGG CAC TAC TTC AAA GGG CCC AGT
 A   G   Q   N   H   G   K   L   N   G   I   K   W   H   Y   F   K   G   P   S>

     1760          1770          1780          1790          1800
 *             *             *             *             *
TAC TCC TTA CGT TCC ACA ACT ATG ATG ATT CGA CCT TTA GAT TTT TGA
 Y   S   L   R   S   T   T   M   M   I   R   P   L   D   F   *>

 1810       1820       1830       1840
  *          *          *          *
AAGCGCAATGTCAGAAGCGATTATGAAAGCAACA

      1850       1860       1870       1880       1890       1900       1910       1920
        *          *          *          *          *          *          *          *
AAGAAATCCGGAGAAGCTGCCAGGTGAGAAACTGTTTGAAAACTTCAGAAGCAAACAATATTGTCTCCCTTCCAGCAATA

      1930       1940       1950       1960       1970       1980       1990       2000
        *          *          *          *          *          *          *          *
AGTGGTAGTTATGTGAAGTCACCAAGGTTCTTGACCGTGAATCTGGAGCCGTTTGAGTTCACAAGAGTCTCTACTTGGGG

      2010       2020       2030       2040       2050       2060       2070       2080
        *          *          *          *          *          *          *          *
TGACAGTGCTCACGTGGCTCGACTATAGAAAACTCCACTGACTGTCGGGCTTTAAAAAGGGAAGAAACTGCTGAGCTTGC

      2090       2100       2110       2120       2130       2140
        *          *          *          *          *          *
TGTGCTTCAAACTACTACTGGACCTTATTTTGGAACTATGGTAGCCAGATGATAAATATGGTTAATTTC
```

Fig. 5A

```
          10         20         30         40         50         60         70         80
           *          *          *          *          *          *          *          *
CAGCTGACTCAGGCAGGCTCCATGCTGAACGGTCACACAGAGAGGAAACAATAAATCTCAGCTACTATGCAATAAATATC

          90         100        110        120        130        140        150        160
           *          *          *          *          *          *          *          *
TCAAGTTTTAACGAAGAAAAACATCATTGCAGTGAAATAAAAAATTTTAAAATTTTAGAACAAAGCTAACAAATGGCTAG

         170        180        190        200        210        220        230        240
           *          *          *          *          *          *          *          *
TTTTCTATGATTCTTCTTCAAACGCTTTCTTTGAGGGGGAAAGAGTCAAACAAACAAGCAGTTTTACCTGAAATAAAGAA

         250        260        270        280        290        300        310
           *          *          *          *          *          *          *
CTAGTTTTAGAGGTCAGAAGAAAGGAGCAAGTTTTGCGAGAGGCACGGAAGGAGTGTGCTGGCAGTACA ATG ACA GTT
                                                                        M   T   V>

320        330        340        350        360        370
 *          *          *          *          *          *
TTC CTT TCC TTT GCT TTC CTC GCT GCC ATT CTG ACT CAC ATA GGG TGC AGC AAT CAG CGC
 F   L   S   F   A   F   L   A   A   I   L   T   H   I   G   C   S   N   Q   R>

380        390        400        410        420        430
 *          *          *          *          *          *
CGA AGT CCA GAA AAC AGT GGG AGA AGA TAT AAC CGG ATT CAA CAT GGG CAA TGT GCC TAC
 R   S   P   E   N   S   G   R   R   Y   N   R   I   Q   H   G   Q   C   A   Y>
```

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Fig. 5B

```
440                 450                 460                 470                 480                 490
*                   *                   *                   *                   *                   *
ACT TTC ATT CTT CCA GAA CAC GAT GGC AAC TGT CGT GAG AGT ACG ACA GAC CAG TAC AAC
 T   F   I   L   P   E   H   D   G   N   C   R   E   S   T   T   D   Q   Y   N>

500                 510                 520                 530                 540                 550
*                   *                   *                   *                   *                   *
ACA AAC GCT CTG CAG AGA GAT GCT CCA CAC GTG GAA CCG GAT TTC TCT TCC CAG AAA CTT
 T   N   A   L   Q   R   D   A   P   H   V   E   P   D   F   S   S   Q   K   L>

560                 570                 580                 590                 600                 610
*                   *                   *                   *                   *                   *
CAA CAT CTG GAA CAT GTG ATG GAA AAT TAT ACT CAG TGG CTG CAA AAA CTT GAG AAT TAC
 Q   H   L   E   H   V   M   E   N   Y   T   Q   W   L   Q   K   L   E   N   Y>

620                 630                 640                 650                 660                 670
*                   *                   *                   *                   *                   *
ATT GTG GAA AAC ATG AAG TCG GAG ATG GCC CAG ATA CAG CAG AAT GCA GTT CAG AAC CAC
 I   V   E   N   M   K   S   E   M   A   Q   I   Q   Q   N   A   V   Q   N   H>

680                 690                 700                 710                 720                 730
*                   *                   *                   *                   *                   *
ACG GCT ACC ATG CTG GAG ATA GGA ACC AGC CTC CTC TCT CAG ACT GCA GAG CAG ACC AGA
 T   A   T   M   L   E   I   G   T   S   L   L   S   Q   T   A   E   Q   T   R>

740                 750                 760                 770                 780                 790
*                   *                   *                   *                   *                   *
AAG CTG ACA GAT GTT GAG ACC CAG GTA CTA AAT CAA ACT TCT CGA CTT GAG ATA CAG CTG
 K   L   T   D   V   E   T   Q   V   L   N   Q   T   S   R   L   E   I   Q   L>
```

Fig. 5C

```
800               810               820               830               840               850
*                 *                 *                 *                 *                 *
CTG GAG AAT TCA TTA TCC ACC TAC AAG CTA GAG AAG CAA CTT CTT CAA CAG ACA AAT GAA
 L   E   N   S   L   S   T   Y   K   L   E   K   Q   L   L   Q   Q   T   N   E>

860               870               880               890               900               910
*                 *                 *                 *                 *                 *
ATC TTG AAG ATC CAT GAA AAA AAC AGT TTA TTA GAA CAT AAA ATC TTA GAA ATG GAA GGA
 I   L   K   I   H   E   K   N   S   L   L   E   H   K   I   L   E   M   E   G>

920               930               940               950               960               970
*                 *                 *                 *                 *                 *
AAA CAC AAG GAA GAG TTG GAC ACC TTA AAG GAA GAG AAA GAG AAC CTT CAA GGC TTG GTT
 K   H   K   E   E   L   D   T   L   K   E   E   K   E   N   L   Q   G   L   V>

980               990               1000              1010              1020              1030
*                 *                 *                 *                 *                 *
ACT CGT CAA ACA TAT ATA ATC CAG GAG CTG GAA AAG CAA TTA AAC AGA GCT ACC ACC AAC
 T   R   Q   T   Y   I   I   Q   E   L   E   K   Q   L   N   R   A   T   T   N>

1040              1050              1060              1070              1080              1090
*                 *                 *                 *                 *                 *
AAC AGT GTC CTT CAG AAG CAG CAA CTG GAG CTG ATG GAC ACA GTC CAC AAC CTT GTC AAT
 N   S   V   L   Q   K   Q   Q   L   E   L   M   D   T   V   H   N   L   V   N>

1100              1110              1120              1130              1140              1150
*                 *                 *                 *                 *                 *
CTT TGC ACT AAA GAA GTT TTA CTA AAG GGA GGA AAA AGA GAG GAA GAG AAA CCA TTT AGA
 L   C   T   K   E   V   L   L   K   G   G   K   R   E   E   E   K   P   F   R>
```

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Fig. 5D

```
1160        1170        1180        1190        1200        1210
 *           *           *           *           *           *
GAC TGT GCA GAT GTA TAT CAA GCT GGT TTT AAT AAA AGT GGA ATC TAC ACT ATT TAT ATT
 D   C   A   D   V   Y   Q   A   G   F   N   K   S   G   I   Y   T   I   Y   I>

1220        1230        1240        1250        1260        1270
 *           *           *           *           *           *
AAT AAT ATG CCA GAA CCC AAA AAG GTG TTT TGC AAT ATG GAT GTC AAT GGG GGA GGT TGG
 N   N   M   P   E   P   K   K   V   F   C   N   M   D   V   N   G   G   G   W>

1280        1290        1300        1310        1320        1330
 *           *           *           *           *           *
ACT GTA ATA CAA CAT CGT GAA GAT GGA AGT CTA GAT TTC CAA AGA GGC TGG AAG GAA TAT
 T   V   I   Q   H   R   E   D   G   S   L   D   F   Q   R   G   W   K   E   Y>

1340        1350        1360        1370        1380        1390
 *           *           *           *           *           *
AAA ATG GGT TTT GGA AAT CCC TCC GGT GAA TAT TGG CTG GGG AAT GAG TTT ATT TTT GCC
 K   M   G   F   G   N   P   S   G   E   Y   W   L   G   N   E   F   I   F   A>

1400        1410        1420        1430        1440        1450
 *           *           *           *           *           *
ATT ACC AGT CAG AGG CAG TAC ATG CTA AGA ATT GAG TTA ATG GAC TGG GAA GGG AAC CGA
 I   T   S   Q   R   Q   Y   M   L   R   I   E   L   M   D   W   E   G   N   R>

1460        1470        1480        1490        1500        1510
 *           *           *           *           *           *
GCC TAT TCA CAG TAT GAC AGA TTC CAC ATA GGA AAT GAA AAG CAA AAC TAT AGG TTG TAT
 A   Y   S   Q   Y   D   R   F   H   I   G   N   E   K   Q   N   Y   R   L   Y>
```

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Fig. 5E

```
1520          1530          1540          1550          1560          1570
 *             *             *             *             *             *
 TTA AAA GGT CAC ACT GGG ACA GCA GGA AAA CAG AGC AGC CTG ATC TTA CAC GGT GCT GAT
  L   K   G   H   T   G   T   A   G   K   Q   S   S   L   I   L   H   G   A   D>

1580          1590          1600          1610          1620          1630
 *             *             *             *             *             *
 TTC AGC ACT AAA GAT GCT GAT AAT GAC AAC TGT ATG TGC AAA TGT GCC CTC ATG TTA ACA
  F   S   T   K   D   A   D   N   D   N   C   M   C   K   C   A   L   M   L   T>

1640          1650          1660          1670          1680          1690
 *             *             *             *             *             *
 GGA GGA TGG TGG TTT GAT GCT TGT GGC CCC TCC AAT CTA AAT GGA ATG TTC TAT ACT GCG
  G   G   W   W   F   D   A   C   G   P   S   N   L   N   G   M   F   Y   T   A>

1700          1710          1720          1730          1740          1750
 *             *             *             *             *             *
 GGA CAA AAC CAT GGA AAA CTG AAT GGG ATA AAG TGG CAC TAC TTC AAA GGG CCC AGT TAC
  G   Q   N   H   G   K   L   N   G   I   K   W   H   Y   F   K   G   P   S   Y>

1760          1770          1780          1790          1800
 *             *             *             *             *
 TCC TTA CGT TCC ACA ACT ATG ATG ATT CGA CCT TTA GAT TTT TGA
  S   L   R   S   T   T   M   M   I   R   P   L   D   F   *>
```

Fig. 5F

```
    1810        1820        1830        1840
     *           *           *           *
AAGCGCAATGTCAGAAGCGATTATGAAAGCAACAAAG

          1850        1860        1870        1880        1890        1900        1910        1920
           *           *           *           *           *           *           *           *
AAATCCGGAGAAGCTGCCAGGTGAGAAACTGTTTGAAAACTTCAGAAGCAAACAATATTGTCTCCCTTCCAGCAATAAGT

          1930        1940        1950        1960        1970        1980        1990        2000
           *           *           *           *           *           *           *           *
GGTAGTTATGTGAAGTCACCAAGGTTCTTGACCGTGAATCTGGAGCCGTTTGAGTTCACAAGAGTCTCTACTTGGGGTGA

          2010        2020        2030        2040        2050        2060        2070        2080
           *           *           *           *           *           *           *           *
CAGTGCTCACGTGGCTCGACTATAGAAAACTCCACTGACTGTCGGGCTTTAAAAAGGGAAGAAACTGCTGAGCTTGCTGT

          2090        2100        2110        2120        2130        2140
           *           *           *           *           *           *
GCTTCAAACTACTACTGGACCTTATTTTGGAACTATGGTAGCCAGATGATAAATATGGTTAATTTC
```

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Fig. 6A

```
          10         20         30         40         50         60         70         80
           *          *          *          *          *          *          *          *
GAATTCCTGGGTTGGTGTTTATCTCCTCCCAGCCTTGAGGGAGGGAACAACACTGTAGGATCTGGGGAGAGAGGAACAAA

          90        100        110        120        130        140        150        160
           *          *          *          *          *          *          *          *
GGACCGTGAAAGCTGCTCTGTAAAAGCTGACACAGCCCTCCCAAGTGAGCAGGACTGTTCTTCCCACTGCAATCTGACAG

         170        180        190        200        210        220        230        240
           *          *          *          *          *          *          *          *
TTTACTGCATGCCTGGAGAGAACACAGCAGTAAAAACCAGGTTTGCTACTGGAAAAAGAGGAAAGAGAAGACTTTCATTG

         250        260        270        280        290        300        310        320
           *          *          *          *          *          *          *          *
ACGGACCCAGCCATGGCAGCGTAGCAGCCCTGCGTTTCAGACGGCAGCAGCTCGGGACTCTGGACGTGTGTTTGCCCTCA

         330        340        350        360        370        380
           *          *          *          *          *          *
AGTTTGCTAAGCTGCTGGTTTATTACTGAAGAAAGA ATG TGG CAG ATT GTT TTC TTT ACT CTG AGC TGT
                                       M   W   Q   I   V   F   F   T   L   S   C>

390        400        410        420        430        440
 *          *          *          *          *          *
GAT CTT GTC TTG GCC GCA GCC TAT AAC AAC TTT CGG AAG AGC ATG GAC AGC ATA GGA AAG
 D   L   V   L   A   A   A   Y   N   N   F   R   K   S   M   D   S   I   G   K>

450        460        470        480        490        500
 *          *          *          *          *          *
AAG CAA TAT CAG GTC CAG CAT GGG TCC TGC AGC TAC ACT TTC CTC CTG CCA GAG ATG GAC
 K   Q   Y   Q   V   Q   H   G   S   C   S   Y   T   F   L   L   P   E   M   D>
```

Fig. 6B

```
510                     520                     530                       540                     550                     560
 *                       *                       *                         *                       *                       *
AAC  TGC  CGC  TCT  TCC  TCC  AGC  CCC  TAC  GTG  TCC  AAT  GCT  GTG  CAG  AGG  GAC  GCG  CCG  CTC
 N    C    R    S    S    S    S    P    Y    V    S    N    A    V    Q    R    D    A    P    L>

570                     580                     590                       600                     610                     620
 *                       *                       *                         *                       *                       *
GAA  TAC  GAT  GAC  TCG  GTG  CAG  AGG  CTG  CAA  GTG  CTG  GAG  AAC  ATC  ATG  GAA  AAC  AAC  ACT
 E    Y    D    D    S    V    Q    R    L    Q    V    L    E    N    I    M    E    N    N    T>

630                     640                     650                       660                     670                     680
 *                       *                       *                         *                       *                       *
CAG  TGG  CTA  ATG  AAG  CTT  GAG  AAT  TAT  ATC  CAG  GAC  AAC  ATG  AAG  AAA  GAA  ATG  GTA  GAG
 Q    W    L    M    K    L    E    N    Y    I    Q    D    N    M    K    K    E    M    V    E>

690                     700                     710                       720                     730                     740
 *                       *                       *                         *                       *                       *
ATA  CAG  CAG  AAT  GCA  GTA  CAG  AAC  CAG  ACG  GCT  GTG  ATG  ATA  GAA  ATA  GGG  ACA  AAC  CTG
 I    Q    Q    N    A    V    Q    N    Q    T    A    V    M    I    E    I    G    T    N    L>

750                     760                     770                       780                     790                     800
 *                       *                       *                         *                       *                       *
TTG  AAC  CAA  ACA  GCT  GAG  CAA  ACG  CGG  AAG  TTA  ACT  GAT  GTG  GAA  GCC  CAA  GTA  TTA  AAT
 L    N    Q    T    A    E    Q    T    R    K    L    T    D    V    E    A    Q    V    L    N>

810                     820                     830                       840                     850                     860
 *                       *                       *                         *                       *                       *
CAG  ACC  ACG  AGA  CTT  GAA  CTT  CAG  CTC  TTG  GAA  CAC  TCC  CTC  TCG  ACA  AAC  AAA  TTG  GAA
 Q    T    T    R    L    E    L    Q    L    L    E    H    S    L    S    T    N    K    L    E>
```

Fig. 6C

```
870               880               890               900               910               920
*                 *                 *                 *                 *                 *
AAA CAG ATT TTG GAC CAG ACC AGT GAA ATA AAC AAA TTG CAA GAT AAG AAC AGT TTC CTA
 K   Q   I   L   D   Q   T   S   E   I   N   K   L   Q   D   K   N   S   F   L>

930               940               950               960               970               980
*                 *                 *                 *                 *                 *
GAA AAG AAG GTG CTA GCT ATG GAA GAC AAG CAC ATC ATC CAA CTA CAG TCA ATA AAA GAA
 E   K   K   V   L   A   M   E   D   K   H   I   I   Q   L   Q   S   I   K   E>

990               1000              1010              1020              1030              1040
*                 *                 *                 *                 *                 *
GAG AAA GAT CAG CTA CAG GTG TTA GTA TCC AAG CAA AAT TCC ATC ATT GAA GAA CTA GAA
 E   K   D   Q   L   Q   V   L   V   S   K   Q   N   S   I   I   E   E   L   E>

1050              1060              1070              1080              1090              1100
*                 *                 *                 *                 *                 *
AAA AAA ATA GTG ACT GCC ACG GTG AAT AAT TCA GTT CTT CAA AAG CAG CAA CAT GAT CTC
 K   K   I   V   T   A   T   V   N   N   S   V   L   Q   K   Q   Q   H   D   L>

1110              1120              1130              1140              1150              1160
*                 *                 *                 *                 *                 *
ATG GAG ACA GTT AAT AAC TTA CTG ACT ATG ATG TCC ACA TCA AAC TCA GCT AAG GAC CCC
 M   E   T   V   N   N   L   L   T   M   M   S   T   S   N   S   A   K   D   P>

1170              1180              1190              1200              1210              1220
*                 *                 *                 *                 *                 *
ACT GTT GCT AAA GAA GAA CAA ATC AGC TTC AGA GAC TGT GCT GAA GTA TTC AAA TCA GGA
 T   V   A   K   E   E   Q   I   S   F   R   D   C   A   E   V   F   K   S   G>
```

Fig. 6D

```
1230        1240        1250        1260        1270        1280
 *           *           *           *           *           *
CAC ACC ACA AAT GGC ATC TAC ACG TTA ACA TTC CCT AAT TCT ACA GAA GAG ATC AAG GCC
 H   T   T   N   G   I   Y   T   L   T   F   P   N   S   T   E   E   I   K   A>

1290        1300        1310        1320        1330        1340
 *           *           *           *           *           *
TAC TGT GAC ATG GAA GCT GGA GGA GGC GGG TGG ACA ATT ATT CAG CGA CGT GAG GAT GGC
 Y   C   D   M   E   A   G   G   G   G   W   T   I   I   Q   R   R   E   D   G>

1350        1360        1370        1380        1390        1400
 *           *           *           *           *           *
AGC GTT GAT TTT CAG AGG ACT TGG AAA GAA TAT AAA GTG GGA TTT GGT AAC CCT TCA GGA
 S   V   D   F   Q   R   T   W   K   E   Y   K   V   G   F   G   N   P   S   G>

1410        1420        1430        1440        1450        1460
 *           *           *           *           *           *
GAA TAT TGG CTG GGA AAT GAG TTT GTT TCG CAA CTG ACT AAT CAG CAA CGC TAT GTG CTT
 E   Y   W   L   G   N   E   F   V   S   Q   L   T   N   Q   Q   R   Y   V   L>

1470        1480        1490        1500        1510        1520
 *           *           *           *           *           *
AAA ATA CAC CTT AAA GAC TGG GAA GGG AAT GAG GCT TAC TCA TTG TAT GAA CAT TTC TAT
 K   I   H   L   K   D   W   E   G   N   E   A   Y   S   L   Y   E   H   F   Y>

1530        1540        1550        1560        1570        1580
 *           *           *           *           *           *
CTC TCA AGT GAA GAA CTC AAT TAT AGG ATT CAC CTT AAA GGA CTT ACA GGG ACA GCC GGC
 L   S   S   E   E   L   N   Y   R   I   H   L   K   G   L   T   G   T   A   G>
```

Fig. 6E

```
1590          1600          1610          1620          1630          1640
 *             *             *             *             *             *
 AAA ATA AGC AGC ATC AGC CAA CCA GGA AAT GAT TTT AGC ACA AAG GAT GGA GAC AAC GAC
  K   I   S   S   I   S   Q   P   G   N   D   F   S   T   K   D   G   D   N   D>

1650          1660          1670          1680          1690          1700
 *             *             *             *             *             *
 AAA TGT ATT TGC AAA TGT TCA CAA ATG CTA ACA GGA GGC TGG TGG TTT GAT GCA TGT GGT
  K   C   I   C   K   C   S   Q   M   L   T   G   G   W   W   F   D   A   C   G>

1710          1720          1730          1740          1750          1760
 *             *             *             *             *             *
 CCT TCC AAC TTG AAC GGA ATG TAC TAT CCA CAG AGG CAG AAC ACA AAT AAG TTC AAC GGC
  P   S   N   L   N   G   M   Y   Y   P   Q   R   Q   N   T   N   K   F   N   G>

1770          1780          1790          1800          1810          1820
 *             *             *             *             *             *
 ATT AAA TGG TAC TAC TGG AAA GGC TCA GGC TAT TCG CTC AAG GCC ACA ACC ATG ATG ATC
  I   K   W   Y   Y   W   K   G   S   G   Y   S   L   K   A   T   T   M   M   I>

1830          1840
 *             *
 CGA CCA GCA GAT TTC
  R   P   A   D   F>

  1850          1860          1870          1880          1890          1900          1910          1920
   *             *             *             *             *             *             *             *
TAAACATCCCAGTCCACCTGAGGAACTGTCTCGAACTATTTTCAAAGACTTAAGCCCAGTGCACTGAAAGTCACGG
```

Fig. 6F

```
      1930       1940       1950       1960       1970       1980       1990       2000
        *          *          *          *          *          *          *          *
CTGCGCACTGTGTCCTCTTCCACCACAGAGGGCGTGTGCTCGGTGCTGACGGGACCCACATGCTCCAGATTAGAGCCTGT

       2010       2020       2030       2040       2050       2060       2070       2080
        *          *          *          *          *          *          *          *
AAACTTTATCACTTAAACTTGCATCACTTAACGGACCAAAGCAAGACCCTAAACATCCATAATTGTGATTAGACAGAACA

       2090       2100       2110       2120       2130       2140       2150       2160
        *          *          *          *          *          *          *          *
CCTATGCAAAGATGAACCCGAGGCTGAGAATCAGACTGACAGTTTACAGACGCTGCTGTCACAACCAAGAATGTTATGTG

       2170       2180       2190       2200       2210       2220       2230       2240
        *          *          *          *          *          *          *          *
CAAGTTTATCAGTAAATAACTGGAAAACAGAACACTTATGTTATACAATACAGATCATCTTGGAACTGCATTCTTCTGAG

       2250       2260       2270       2280
        *          *          *          *
CACTGTTTATACACTGTGTAAATACCCATATGTCCTGAATTC
```

Fig.7.

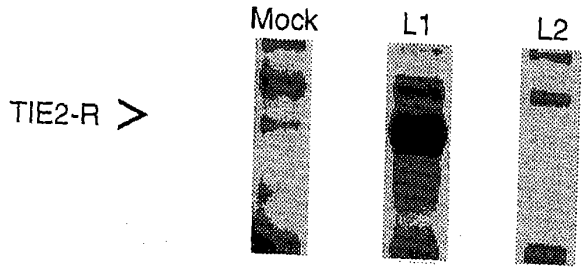


Fig.8.

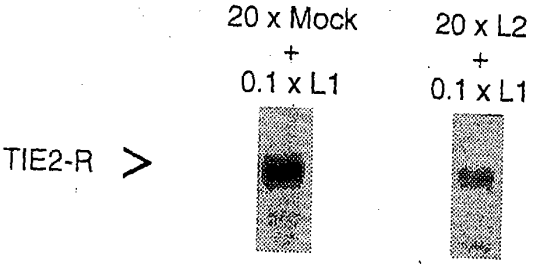


Fig.9.

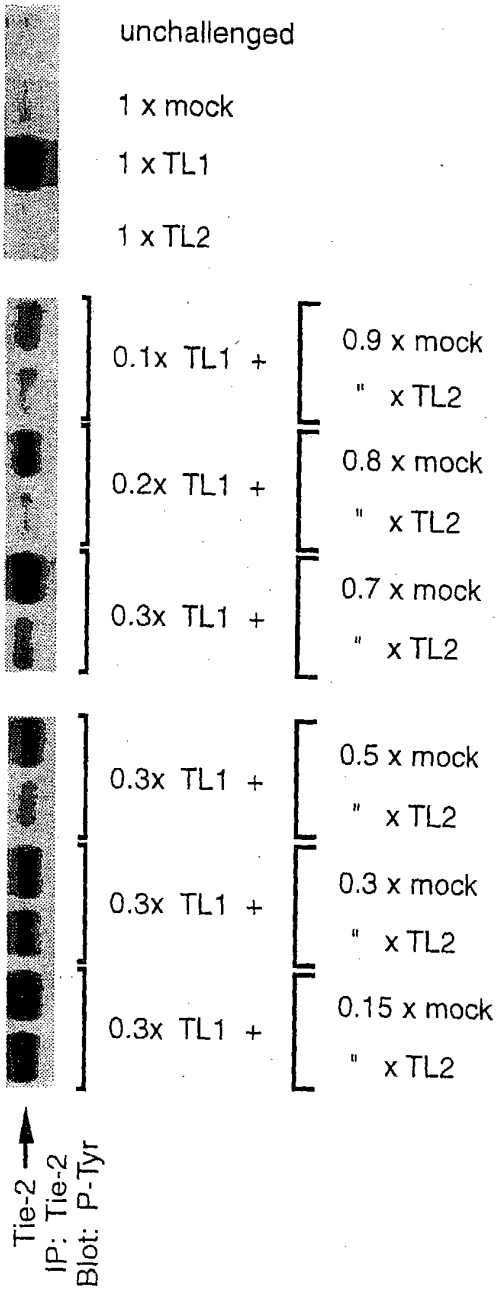

unchallenged
1 x mock
1 x TL1
1 x TL2
0.1x TL1 +
0.9 x mock
" x TL2
0.2x TL1 +
0.8 x mock
" x TL2
0.3x TL1 +
0.7 x mock
" x TL2
0.3x TL1 +
0.5 x mock
" x TL2
0.3x TL1 +
0.3 x mock
" x TL2
0.3x TL1 +
0.15 x mock
" x TL2
Tie-2
IP: Tie-2
Blot: P-Tyr

Fig.10.

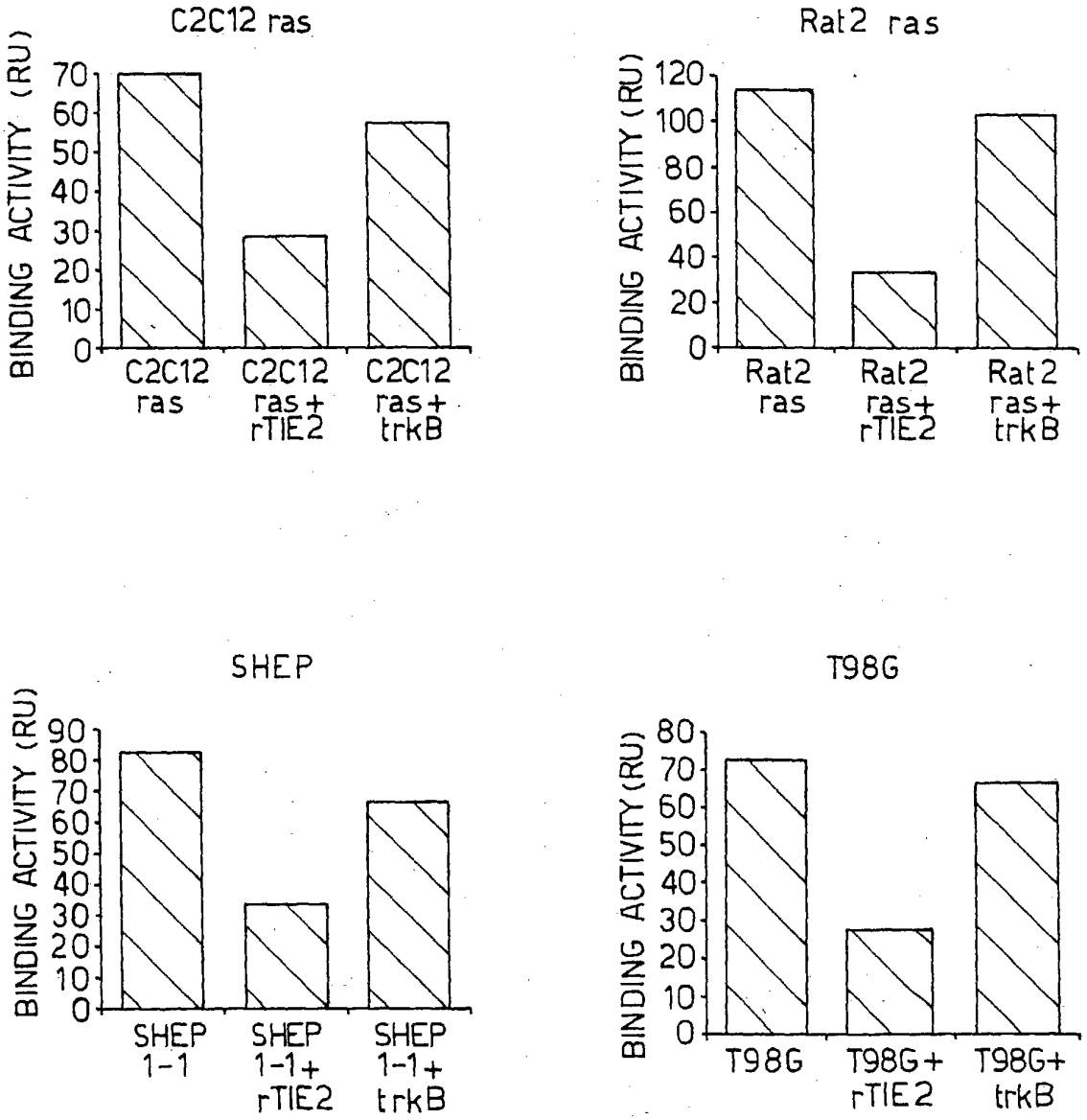
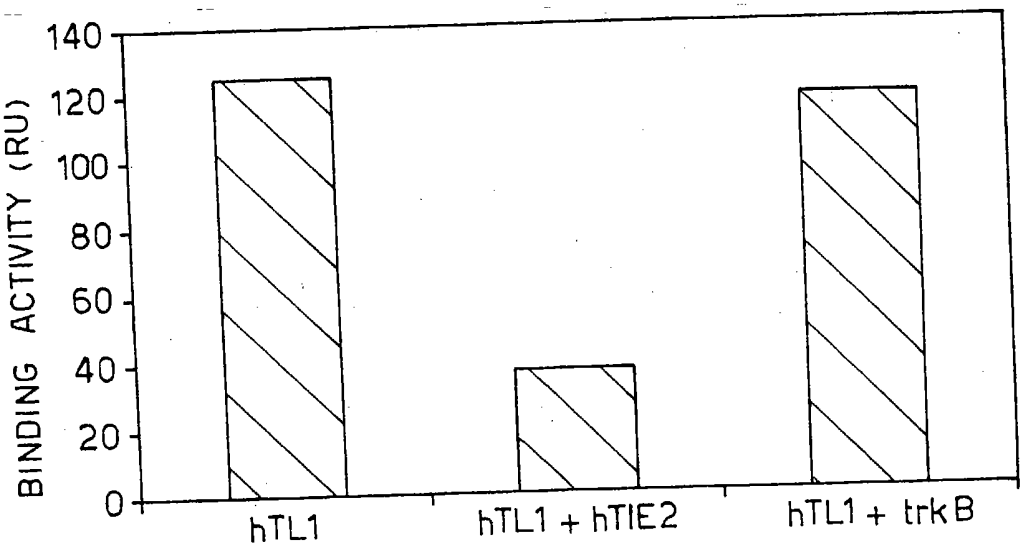

C2C12 ras
BINDING ACTIVITY (RU)
0
10
20
30
40
50
60
70
C2C12 ras
C2C12 ras+ rTIE2
C2C12 ras+ trkB
Rat2 ras
BINDING ACTIVITY (RU)
0
20
40
60
80
100
120
Rat2 ras
Rat2 ras+ rTIE2
Rat2 ras+ trkB
SHEP
BINDING ACTIVITY (RU)
0
10
20
30
40
50
60
70
80
90
SHEP 1-1
SHEP 1-1+ rTIE2
SHEP 1-1+ trkB
T98G
BINDING ACTIVITY (RU)
0
10
20
30
40
50
60
70
80
T98G
T98G+ rTIE2
T98G+ trkB

Fig.11.


BINDING ACTIVITY (RU)
140
120
100
80
60
40
20
0
hTL1
hTL1 + hTIE2
hTL1 + trk B

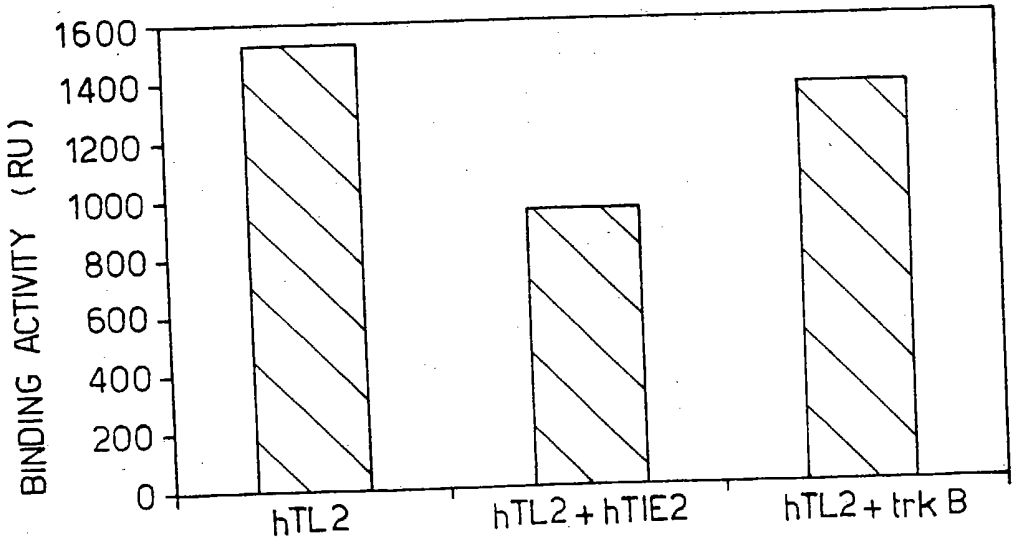

BINDING ACTIVITY (RU)
1600
1400
1200
1000
800
600
400
200
0
hTL2
hTL2 + hTIE2
hTL2 + trk B

Fig.12.

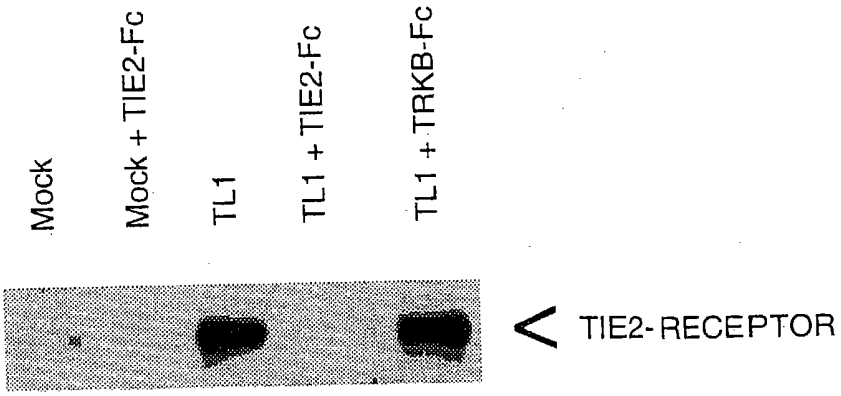
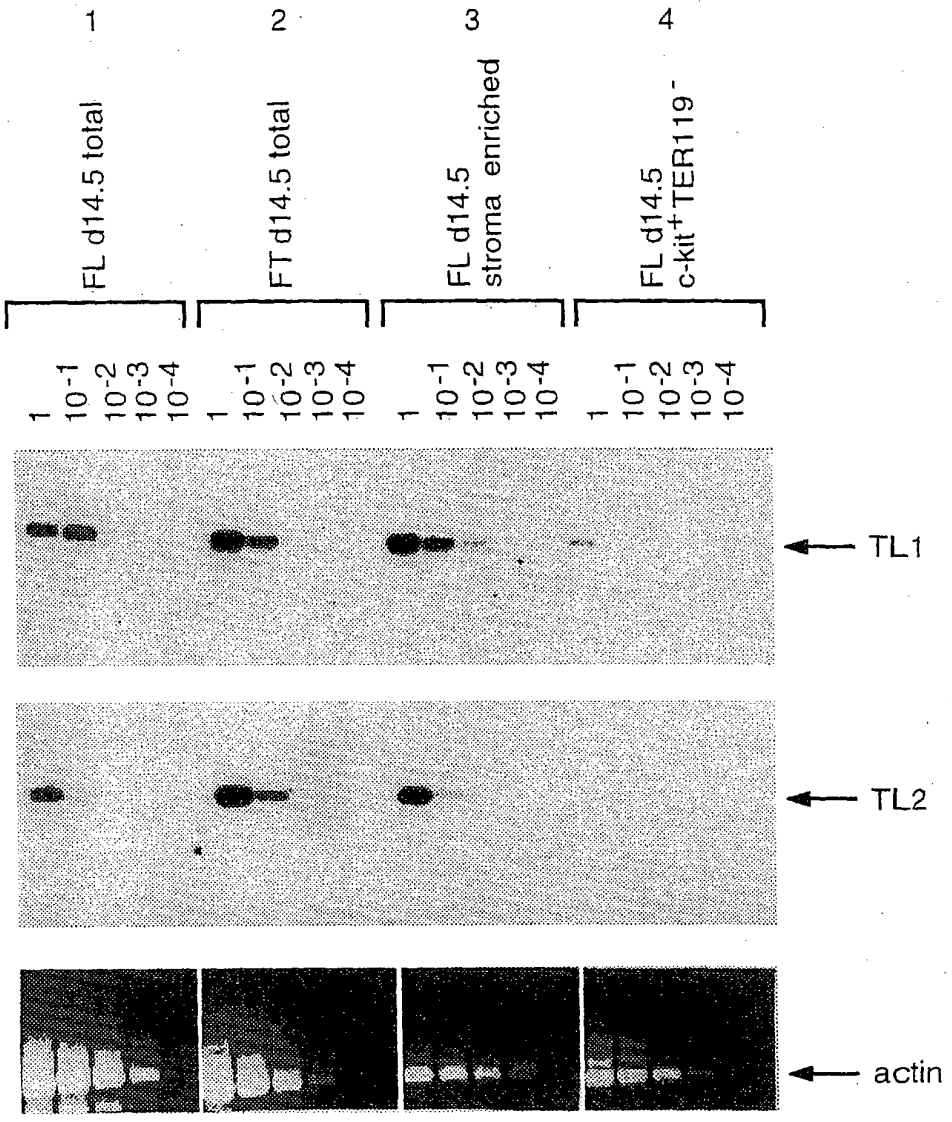
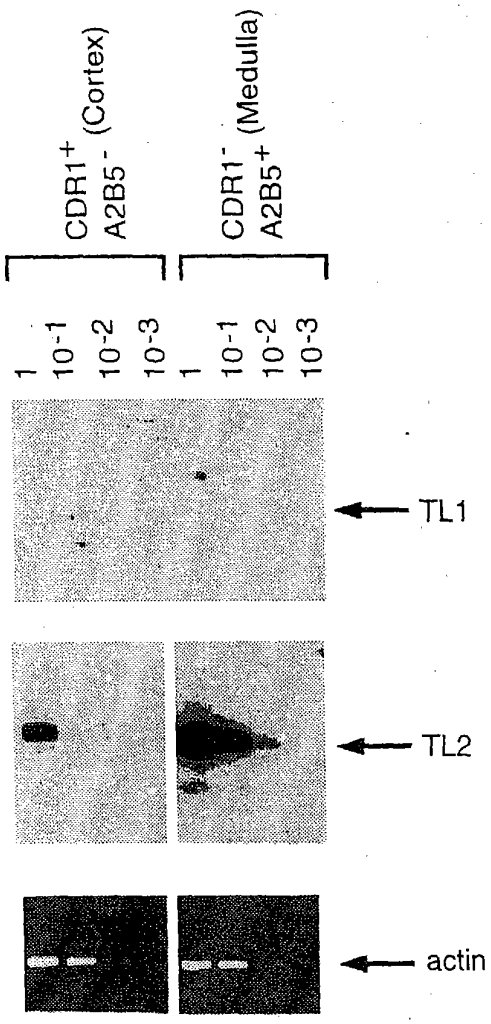


Fig.13.



FL: Fetal Liver

Fig.14.



Fetal Thymus E17.5

$CDR1^+$: Cortical stromal cells

$A2B5^+$: Medulla stromal cells

Fig.15.

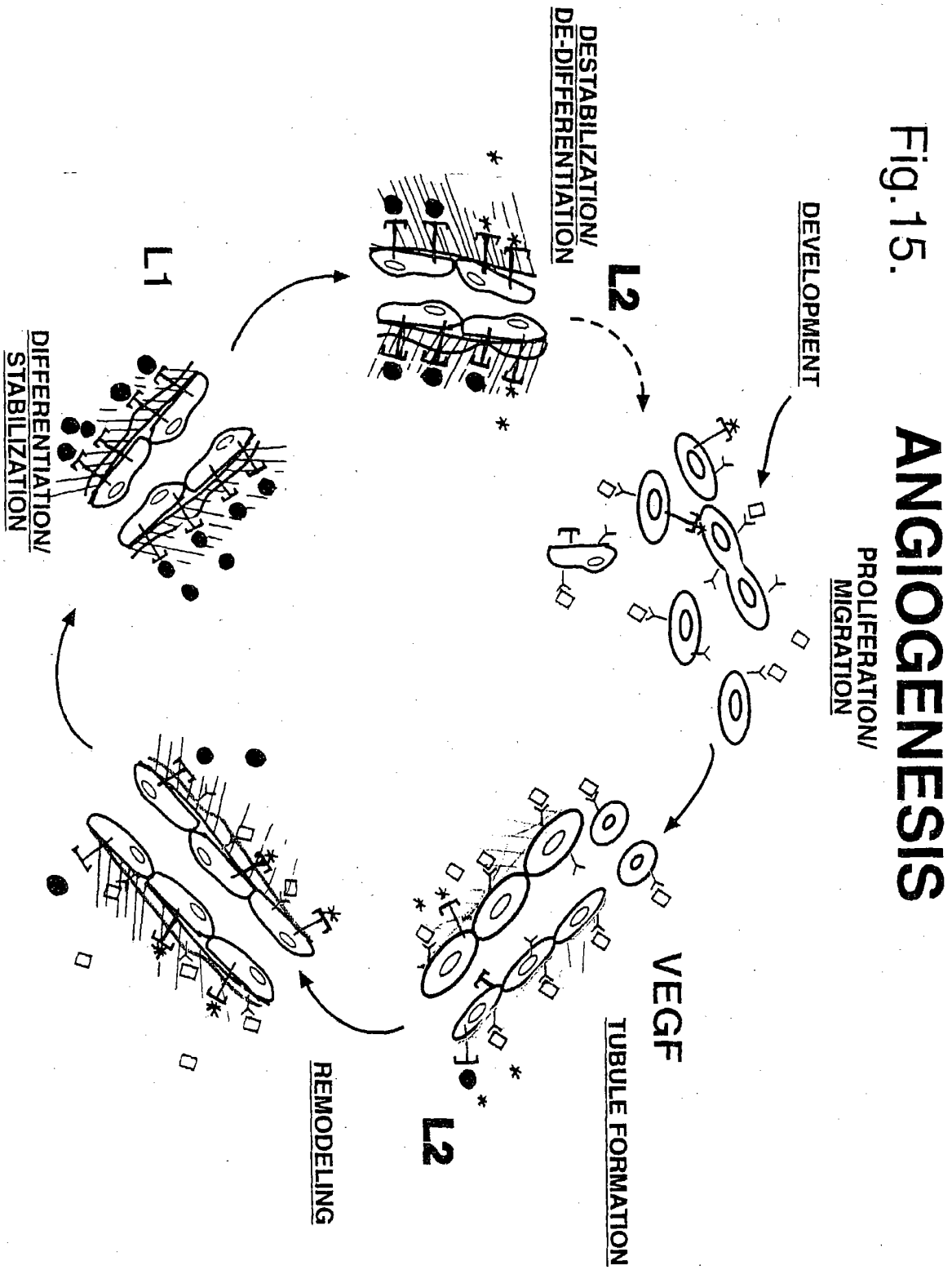

ANGIOGENESIS
DEVELOPMENT
PROLIFERATION/
MIGRATION
VEGF
TUBULE FORMATION
REMODELING
L2
DESTABILIZATION/
DE-DIFFERENTIATION
L2
DIFFERENTIATION/
STABILIZATION
L1

Fig.16.

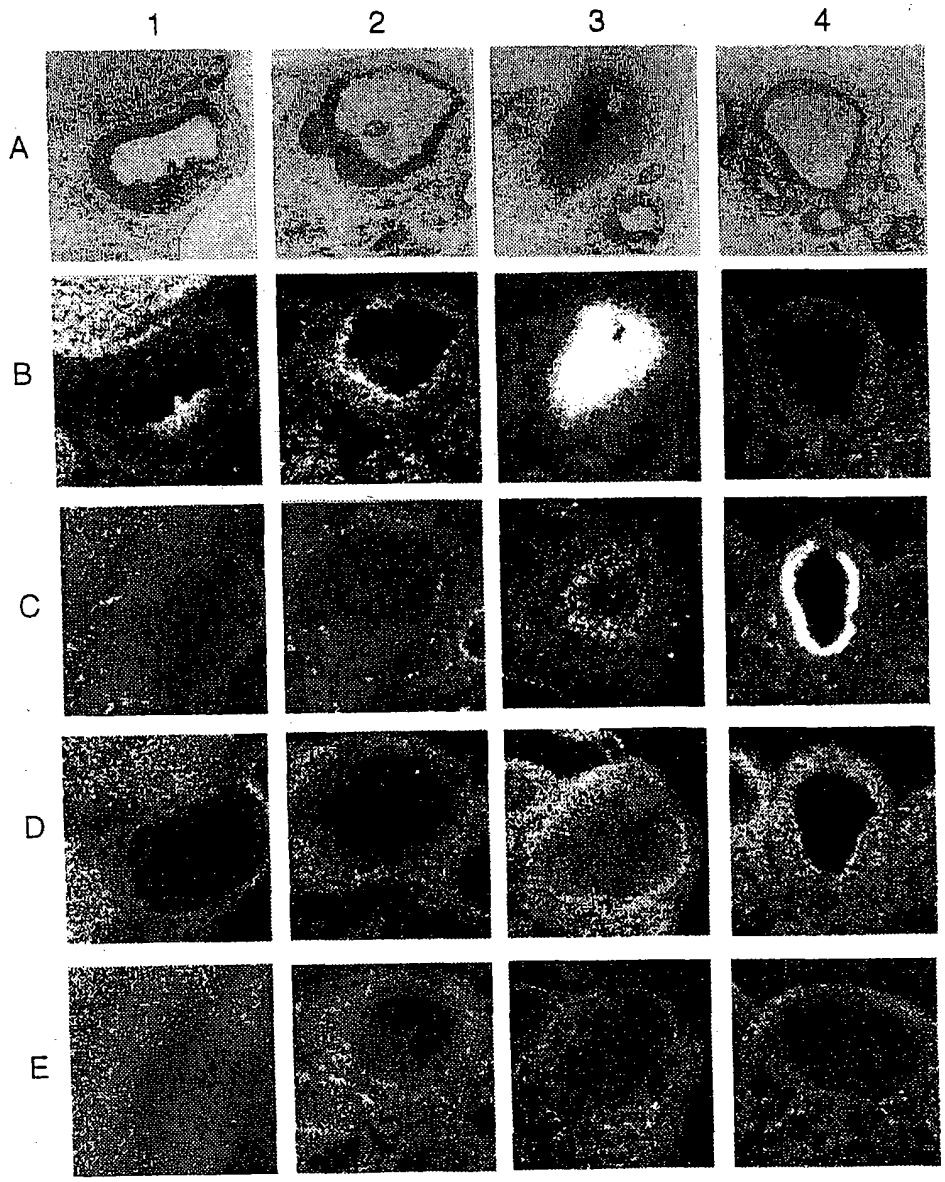


Fig.17.

ENGINEERING OF TIE2 "LIGAND-BODIES"

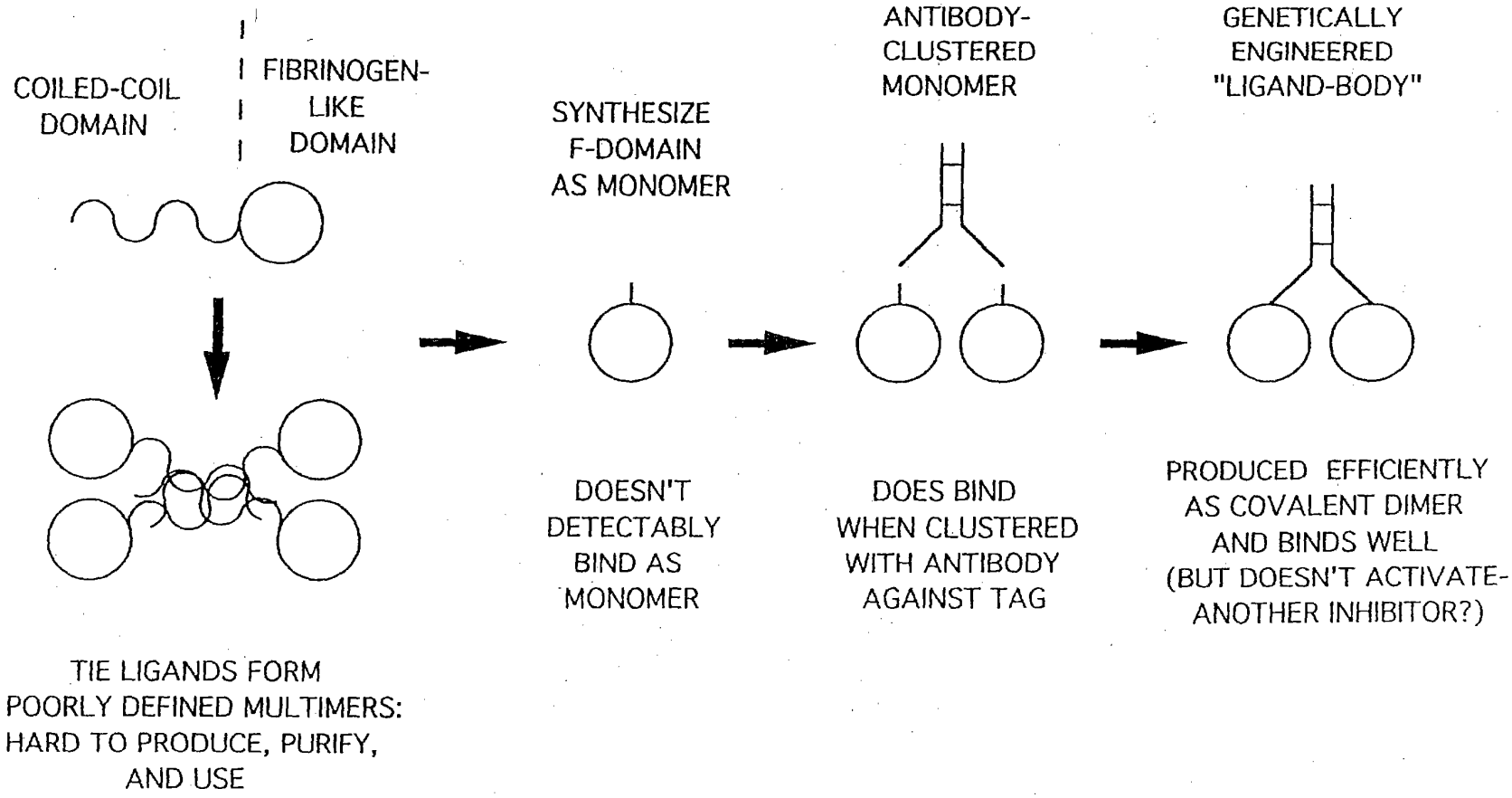


Fig.18.

COVALENT MULTIMERIC STRUCTURE OF
TL1 AND TL2 AND THEIR INTERCONVERSION
BY THE MUTATION OF ONE CYSTEINE

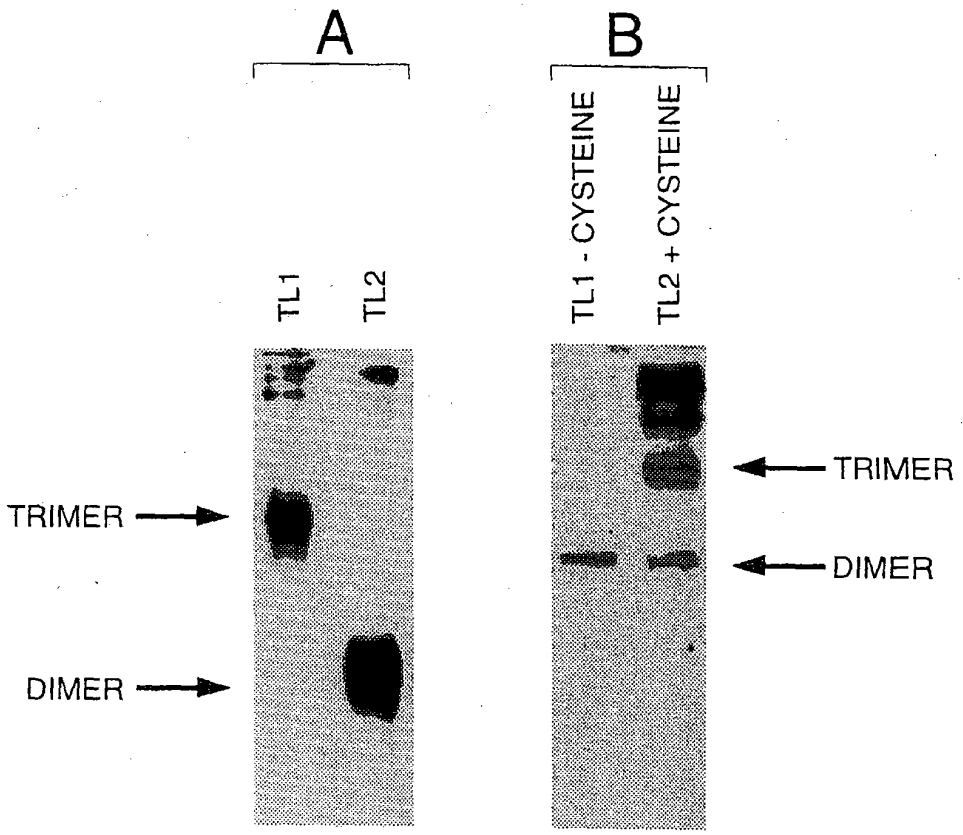


Fig.19. TIE2-IgG binding to immobilized TL1

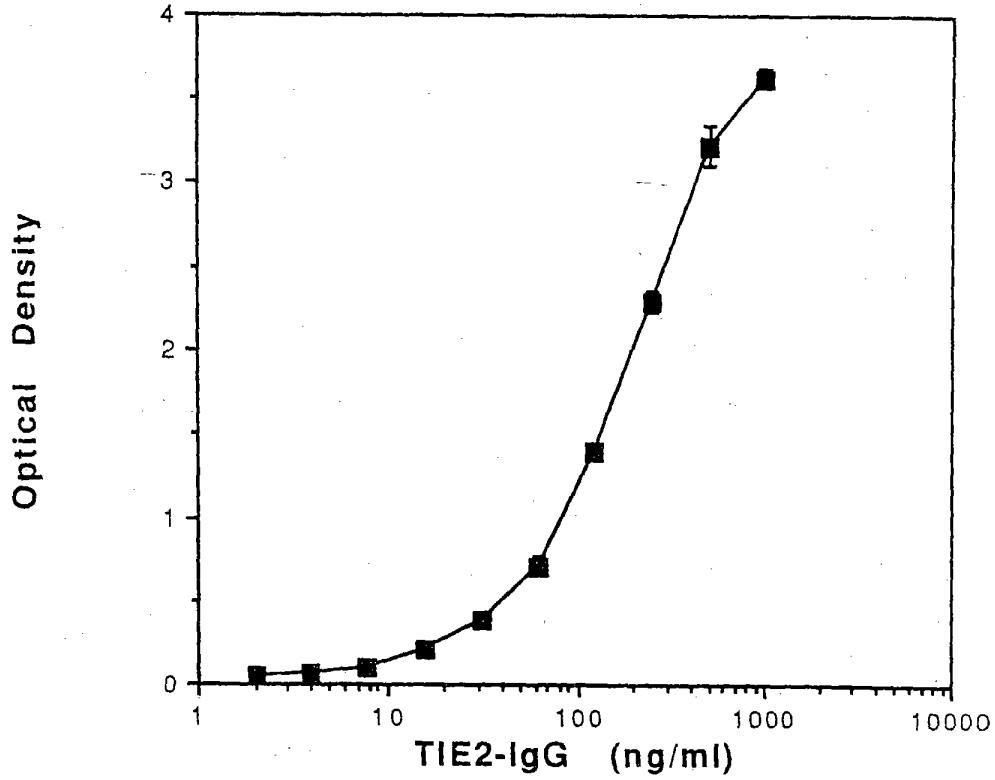


Fig.20. TL1-f-Fc binding to immobilized Tie2 ectodomain